REMARKS

I. Status of the claims

Claims 1-18 are pending. Claims 13-16 have been cancelled without prejudice or disclaimer. Of course, Applicants reserve the right to file one or more continuing applications to the cancelled subject matter. Claims 1, 8, 9, 17, and 18 have been amended. Claim 1 has been amended to recite that at least one of the tonicity modifiers in the PTH formulation is sodium chloride ("NaCl"). Claim 8 has been amended to clarify that the formulation may further comprise mannitol as a tonicity modifier. Claim 9 has been rewritten in independent form. Claims 17 and 18 have been amended to avoid reference to the word "prevention" for the reasons elaborated upon below.

Claims 19-36 have been added. All of the new claims are supported by the originally-filed application. Claims 19-23 further limit the formulation claimed in independent claim 9, by further characterizing the parathyroid hormone, and by reciting that the formulation further comprises a preservative. The "preservative" element is incorporated into new independent claim 24. The preservative may be benzyl alchohol, m-cresol, or EDTA, as taught at page 5, line 30, and page 16, Table VI. Claims dependent therefrom, *i.e.*, 25-28, further limit claim 24 in similar fashion to new claims 19-23. Claims 29 and 30 are directed to processes for preparing the inventive PTH formulations. New claim 31 limits the concentration of the NaCl tonicity modifier to a concentration between 2 mg/ml and 5 mg/ml as is described at page 5, line 29. New claims 32-34 further limit claims 1, 9, and 24, to recite that the parathyroid hormone is human recombinant parathyroid hormone (1-84).

II. Summary of the invention

The present invention relates to highly concentrated pharmaceutical formulations of parathyroid hormone for treating and preventing bone disorders, particularly osteoporosis, and methods of making such formulations.

III. Summary of the Office Action

(i) Claims 1-3, 6-8, 10, 11, and 13-18 are rejected under 35 U.S.C. § 112, second paragraph as indefinite;

(ii) Claims 13-18 are rejected under 35 U.S.C. § 112, first paragraph as non-enabling;

(iii) Claims 1-8, and 10-18 are rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 5,496,801 ("Holthuis"); and

(iv) Claims 8 and 9 are rejected under 35 U.S.C. § 103(a) as unpatentable over Holthuis and U.S. Patent No. 5,563,122 ("Endo").

Applicants respectfully disagree with the Examiner's rationale for rejecting the claims and traverse each of the rejections for the reasons that follow below.

IV. Claims 1-3, 6-8, 10, 11, and 13-18 are not indefinite

(a) The Examiner states that it is not clear if the term "above" in the phrase "a concentration of or above 0.3 mg/ml to 10 mg/ml" applies to the 10 mg/ml concentration, and that, therefore, does not provide "the metes and bounds of what is claimed." Applicants have deleted the word "above" from claim 1. Accordingly, the rejection is moot.

(b) The Examiner also rejected claims 13 and 14 because they allegedly do not further limit claim 1; and claims 15 and 16 for failing to recite positive methodological steps. For the purposes of expediting prosecution, Applicants

have cancelled claims 13-16. Accordingly, the rejections of claims 13-16 are moot.

V. Claims 13-18 are enabled

The Examiner rejected claims 13-18 for reciting the word "prevention," alleging that "it is unpredictable if PTH as claimed has the ability to prevent bone disorders . . . the claims are not enabled for prevention of bone disorders." See the last paragraph at page 3 of the Office Action.

Applicants disagree with the Examiner's reason for rejecting the present claims. There is literal support for the term "prevention" in the specification. See, for instance, page 6, line 2, "[T]he pharmaceutical formulations . . . are useful in the treatment and ***prevention*** of bone disorders, in particular osteoporosis" (emphasis added). It is well accepted that PTH can be used to prevent bone disorders, by reducing symptoms or conditions associated with bone loss attributed to those disorders, albeit not at the high dose concentrations taught and claimed in the present application.

Indeed, the Food and Drug Administration published in May 2000, an industry guide entitled, "DEVELOPMENT OF PARATHYROID HORMONE FOR THE **PREVENTION** AND TREATMENT OF OSTEOPOROSIS" (emphasis added). The guide was designed to "evaluate the safety and effectiveness of parathyroid hormone (PTH) in the ***prevention*** and treatment of osteoporosis" (emphasis added). The guide was also subsequently published in the Federal Register, Vol. 65, No. 115, June 14, 2000 at page 37936. See Exhibit 1.

Nevertheless, for the sole purpose of expediting prosecution, Applicants have replaced the word "prevention" from claim 17 and deleted it from claim 18. Claim 17 now recites a method for "treating a bone related disorder **or reducing or inhibiting bone loss associated with a bone related disorder**" (emphasis

added). The specification supports such an amendment. See, for example, page 1, lines 25-30, of the specification. There, Applicants state that "[I]n mammals, the balance between bone formation, associated with the activity of osteoblasts, on one hand, and ***bone loss, associated with the activity of osteoclasts, one the other hand, is disturbed in several bone affecting diseases, such as osteoporosis***," (emphasis added). The skilled artisan would understand, after reading the present application in light of such a phrase, that administering parathyroid hormone to a mammal can help alleviate conditions associated with a bone-related disorder afflicting that mammal. For instance, Applicants state at page 1, line 29 that "[P]arathyroid hormone has been shown to have a potential therapeutic role in osteoporosis." The skilled artisan would therefore understand that one such "therapeutic role" of PTH would be to reduce or inhibit the loss of bone material associated with a bone related disorder, such as osteoporosis. Thus, the amended claim 17 is supported by the originally-filed specification.

The word "prevention" has been deleted from claim 18, which now recites a "method according to claim 17, wherein the bone related disorder is osteoporosis." Claims 13-16 have been cancelled.

Accordingly, Applicants believe amended claims 17 and 18 are free from objection and respectfully request that the Examiner withdraw this rejection.

VI. Claims 1-8, and 10-18 are not anticipated

The Examiner rejected claims 1-8 and 10-18 as anticipated by Holthuis. The Examiner alleges that "Holthuis teaches PTH hormone formulations to treat osteoporosis . . . aqueous formulations of PTH . . . containing human PTH(1-84), mannitol and a citrate source as buffering agent."

Applicants respectfully disagree and traverse the rejection. Holthuis does not teach the use of NaCl (sodium chloride) as a tonicity modifier, or a PTH

formulation comprising at least two tonicity modifiers. Accordingly, amended claim 1 recites that the claimed formulation comprises "at least one tonicity modifier that is NaCl." Furthermore, the formulation may comprise more than one tonicity modifier, as is claimed in claim 8, which recites that the formulation further comprises mannitol.

The specification states that the tonicity modifier can be "sorbitol, glycerol, sucrose, or preferably, sodium chloride ***and***/or mannitol" (emphasis added). Accordingly, the present formulation may comprise at least two tonicity modifiers, e.g., sodium chloride and mannitol. Accordingly, the originally-filed specification supports the amended claim.

Nowhere does Holthuis recite the use of sodium chloride in a PTH formulation, nor a PTH formulation comprising at least one tonicity modifier. Accordingly, the present claims are not anticipated, and Applicants respectfully request that the Examiner withdraw this rejection.

VII. Claims 8 and 9 are not obvious

Finally, the Examiner rejects claims 8 and 9 as obvious over Holthuis in light of Endo. According to the Examiner, it would have been obvious to "modify the preparation of Holthuis, by adding a sodium solution as taught by Endo, because Endo teaches that a combination of sodium chloride and sugar achieves a higher stability for a PTH preparation."

Applicants respectfully disagree and traverse the rejection. The prior art, as it relates to the incorporation of sodium chloride in PTH formulations, is inconsistent at the time the present invention was filed. Canadian patent CA 2,234,724, for instance, teaches the direct opposite of Endo. The '724 patent taught that when preparing such PTH formulations, sodium chloride should be ***avoided*** because it induces the formation of PTH dimers. The dimers

elicit undesirable side effects in the recipient of the PTH-sodium chloride formulation. See the paragraph bridging pages 3 and 4 of the '724 patent document: the formulation is "preferably free of chloride ions." Accordingly, before the present invention was filed, the skilled artisan would not be motivated to include sodium chloride in the formulation described by Holthuis, despite the teachings of Endo, because the '724 patent taught that it was undesirable to do so.

Futher, the present invention formulates PTH at very high doses compared to dose concentrations described in the prior art. To the extent that Holthuis teaches high PTH concentrations, it does not teach the impact of sodium chloride on PTH stability. On the other hand, the prior art, as evidenced by the '724 patent, demonstrated that sodium chloride ions can cause undesirable aggregation and precipitation of dimeric PTH from solutions containing NaCl. Indeed, Endo requires that sodium chloride be used in conjunction with a sugar to improve "stability" of PTH. The amount of NaCl added to the PTH formulation must be calculated alongside the amount of sugar added to the same formulation because "[T]he larger the amount of sodium chloride to be added to that of sugar, the more stable the PTH preparation will be." Thus, Endo states that "the amount of sodium chloride to be added can be from about 1/1,000 weight part to 1/5 weight part per weight part of sugar, preferably from about 1/100-1/10 weight part thereof."

Accordingly, from reading Endo, the skilled artisan would not add sodium chloride to the PTH formulation of Holthuis without also including a sugar in the predefined quantities taught by Endo. However, Holthuis teaches that a desired excipient of their PTH preparation, "serves as a cryoprotectant during the freeze-drying process and also as a bulking agent to facilitate dosage formulation" and adds that "[O]f the pharmaceutically acceptable excipients, **the present invention avoids sugars** such as lactose and maltose."

Thus, in light of the contradictory state of the prior art and the combined teachings of Holthuis and Endo, there is no motivation for adding a sodium chloride tonicity modifier to a formulation of high-concentration parathyroid hormone, as is required by the present claims. Accordingly, Applicants respectfully request that the Examiner withdraw this rejection.

VIII. Conclusion

Accordingly, Applicants request that the amendments presented herewith be entered, the accompanying arguments be considered and the claims be allowed to pass to issue. The Examiner is invited to contact the undersigned by telephone if it is thought that a phone interview would expedite an early allowance.

Respectfully submitted,

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By: S. A. Bent

FOLEY & LARDNER
Washington Harbour
3000 K Street, N.W., Suite 500
Washington, D.C. 20007-5109
Telephone: (202) 672-5404
Facsimile: (202) 672-5399

Stephen A. Bent
Attorney for Applicant
Registration No. 29,768

MARKED-UP VERSION OF THE CLAIMS

1. (Once amended) A pharmaceutical formulation comprising human parathyroid hormone at a concentration of [or above] 0.3 mg/ml to 10 mg/ml; a pharmaceutically acceptable buffer having a pH from 4 to 6, and at least one tonicity modifier that is NaCl.

8. (Once amended) The formulation according to claim 1, further comprising a second [the said] tonicity modifier that is [sodium chloride and/or] mannitol.

9. (Twice amended) A pharmaceutical [The] formulation [according to claim 1] comprising 1 to 3 mg/ml parathyroid hormone, 2 to 5 mg/ml NaCl, 20 to 50 mg/ml mannitol, and 5 to 10 mM citrate buffer at a pH between 4 and 6.

17. (Twice amended) A method for treating a bone related disorder or reducing or inhibiting bone loss associated with [treatment or prevention of] a bone related disorder[s], comprising [which comprises] administering to a mammal, including man, in need of such treatment or inhibition, [prevention] an effective amount of the [a] formulation of [according to] claim 1.

18. (Once amended) The method according to claim 17, wherein the bone related disorder is [for treatment or prevention of] osteoporosis.